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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/920,033	08/01/2001	Rosanne M. Crooke	ISPH-0592	5785

7590 01/13/2004

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EXAMINER	
EPPS FORD, JANET L	

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 01/13/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/920,033	CROOKE ET AL.	
	Examiner	Art Unit	
	Janet L. Epps-Ford, Ph.D.	1635	

-- The MAILING DATE of this c mmunication app ars on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 October 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-27* is/are pending in the application.

4a) Of the above claim(s) *15-19* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-14,20-23 and 27* is/are rejected.

7)☒ Claim(s) *24-26* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *10-27-03* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 10-27-03 has been entered.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Response to Amendment

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claim 20 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. (New Matter)

5. Applicants have amended claim 20 to recite "wherein said compound specifically hybridizes with nucleotides 1-128 or nucleotides 149-14121 as set forth in SEQ ID NO: 3 and inhibits the expression of a nucleic acid molecule encoding apolipoprotein B." As support for this amendment, Applicants referred to page 9, 90 and page 91. However, nowhere in the

specification as filed is the range 1-128 or 149-14121 adequately supported. Applicants appeared to have merely amended the instant claims to read around the Tang et al. reference which discloses an antisense oligonucleotide of 20 nucleotides in length that is complementary to the first 20 nucleotides of the apoB open reading frame, and corresponds to the region left out of the claimed range of nucleotides 1-128 or 149-14121. The newly added claim limitations are considered new matter since the specification as filed does not provide proper antecedent basis for these limitations.

Applicant is required to cancel the new matter in the reply to this Office Action.

Claim Rejections - 35 USC § 102

6. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

7. Claim 20 is rejected under 35 U.S.C. 102(b) as being anticipated by Tang et al.

Tang et al. describe the use of antisense oligodeoxynucleotides of 20 nucleotides in length targeted to nucleotides 129-154 of SEQ ID NO:3 of the instant application, to reduce the level of apoplipoprotein expression in cultured liver cells in order to understand its mechanism of action. The method of Tang et al. comprises treating cultured liver cells with synthesized Apo B gene antisense in a 0.9% salt solution and measuring the Apo B100 concentration by RT-PCR. Tang et al. concluded that the ApoB gene antisense oligodeoxynucleotide inhibited Apo B gene expression and reduced Apo B concentration

Since the antisense compound of Tang et al. specifically hybridizes to nucleotides 129-154 of SEQ ID NO: 3, specifically nucleotides 149-154 of SEQ ID NO: 3, the teachings of Tang et al. anticipate instant claim 20 which recites non-catalytic compounds that specifically hybridize to nucleotides 149-14121 of SEQ ID NO: 3.

Claim Rejections - 35 USC § 103

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

9. Claims 1-14, 20-23 and 27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chan et al. (WO 01/12789 A2) in view of Branch, Monia et al., and Agrawal et al.

Chan et al. provide a ribozyme that contains flanking sequences that are complementary to nucleotide sequences flanking the GUA cleavage site at position 6679 of a nucleic acid encoding apolipoprotein B. This ribozyme, RB15, comprises 48 nucleotides in length, see page 2, lines 14-18. RB15 is complementary to the flanking sequences surrounding nucleotide position 6679 of the nucleic acid sequence according to GenBank Accession No. X04506, which corresponds to the published human apoB100 sequence, and is identical to SEQ ID NO: 3 of the instant application. Chan et al. also teach that once RB15 is synthesized, it can be modified to enhance its stability by incorporating 2'-O-methyl groups. According to Chan et al. ribozymes may be administered to cells by a variety of methods, including by encapsulation in liposomes, by iontophoresis or by incorporation into vehicles such as hydrogels, psyclodexdrins, or

microspheres, and may be used either alone, or in conjunction with other agents, e.g. other drugs used to lower cholesterol levels (see page 5, lines 1-21).

However, Chan et al. does not disclose non-catalytic compounds of 8 to 50 nuclobases in length that specifically hybridizes with nucleotides 1-114 or nucleotides 151-14121 as set forth in SEQ ID NO: 3 and inhibits the expression of a nucleic acid molecule encoding apolipoprotein B. Additionally, Chan et al. does not disclose said non-catalytic compounds comprising the various modifications recited in the instant claims, or compositions thereof.

Branch teach that in order to maximize target site specificity the length of antisense oligonucleotides should be 17 base pairs or longer, since sequences of 17 base pairs or more would have a high probability of occurring only once in the haploid human genome (p. 47, para. 5-6). It is noted that the limitation "8 to 50 nucleotides in length" encompasses wherein the oligonucleotide is about 17 base pairs in length.

Monia et al. describe methods for the modulation of expression of the human ras oncogene in a cell comprising the administration of modified antisense oligonucleotides. The oligonucleotides used in the methods of Monia et al. are preferably chimeric oligonucleotides that contain two or more chemically distinct regions, each made up of at least one nucleotide. These oligonucleotides typically contain at least one region of modified nucleotides that confers one or more beneficial properties (such as, for example, increased nuclease resistance, increased uptake into cells, increased binding affinity for the RNA target) and a region that is a substrate for enzymes capable of cleaving RNA: DNA or RNA: RNA hybrids (col. 6, lines 49-67). The modified antisense oligonucleotides used in the *in vitro* inhibition methods of Monia et al. may comprise phosphorothioate internucleoside modifications, a 5-methylcytosine modifed

nucleobase, and may further comprise 2'-methoxyethoxy sugar modifications (col. 7-8). The antisense oligonucleotide modifications disclosed by Monia et al. have been shown to increase both binding affinity of the oligonucleotide for its target and nuclease resistance of the oligonucleotide (col. 6, lines 45-58). Furthermore, Monia et al. teach the use of pharmaceutical carriers to facilitate the uptake of oligonucleotides into cells. These carriers include: ointments, lotions, creams, gels, drops, suppositories, sprays, liquids and powders. Compositions for oral administration include powders or granules, suspensions or solutions in water or non-aqueous media, capsules, sachets, or tablets. Thickeners, flavorings, diluents, emulsifiers, dispersing aids or binders may be desirable. Conventional pharmaceutical carriers, aqueous, powder or oily bases, thickeners and the like may be necessary or desirable. Coated condoms, gloves and the like may also be useful, cationic lipids may be included in the formulation to facilitate oligonucleotide uptake (col. 7, lines 40-67).

Agrawal provides motivation for designing antisense oligonucleotides targeting various regions of a target mRNA, including for example the coding region and the 5'-UTR and 3'-UTR of a target mRNA. According to Agrawal et al. "[I]t is considered preferable, therefore, to screen a number of oligonucleotides that encompass different regions on RNA to identify a set of optimal target sites, including the 5'- and 3'-untranslated regions (UTRs), initiation codon site, coding region and intron-exon junctions." (page 77, 1st para.) Additionally, Agrawal et al. generally states (regarding the feasibility of utilizing antisense technology), "antisense technology has become an essential laboratory tool to study and understand the function of any newly discovered genes in recent years."

It would have been obvious to one of ordinary skill in the art to modify the teachings of Chan et al. to design antisense oligonucleotides of about 17 nucleobases in length (Branch), which specifically hybridize to nucleotides surrounding nucleotide 6679 of SEQ ID NO:3, modifying those antisense oligonucleotides with phosphorothioate linkages, 2'-methoxyethoxy modified sugar residues, and a 5'-methylcytosine modified nucleobase (Monia et al.), in order to maximize target site specificity (Branch), and increase hybridization efficiency as well as maintaining nuclease resistance of said antisense oligonucleotide (Monia et al.). It is noted that antisense oligonucleotides of about 17 nucleobases in length (i.e. 8 to 50 nucleobases), which specifically hybridize to nucleotides surrounding nucleotide 6679 of SEQ ID NO:3 are encompassed by the compounds that specifically hybridize with nucleotides 149-14121 as set forth in SEQ ID NO:3, as recited in the instant claims.

Furthermore, it would have been obvious to one of ordinary skill in the art at the time invention was made to modify the teaching of Chan et al. with the teachings of Monia et al. Chan et al. provide explicit disclosure and motivation for designing a nucleic acid based inhibitor of ApoB mRNA expression. One of ordinary skill in the art would have been motivated to design antisense oligonucleotides of about 17 nucleotides in length targeting Apo B and comprising the modifications taught by Monia et al. since modified oligonucleotides according to the preferred embodiments of Monia et al. possess a high target site specificity and increased cellular uptake in comparison to unmodified antisense oligonucleotides.

Additionally, one of ordinary skill in the art seeking to further understand the role of apolipoprotein B gene expression in cellular processes, would have been motivated to design antisense oligonucleotides targeting the mRNA encoding the *apolipoprotein B* gene, since

according to Agrawal, if the sequence of a gene is known, designing antisense oligonucleotides to target that gene would allow the ordinary skilled artisan to further explore and understand the function of that particular gene. Moreover, it would have been obvious at the time the invention was made to substitute the ribozymes targeting apolipoprotein B mRNA with the non-catalytic antisense compounds according to the present invention, since ribozymes and antisense compounds are both nucleic acid based inhibitors, and both function to reduce the expression of a target mRNA. It would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute one functionally equivalent nucleic acid based inhibitor for another that is to be used for the same purpose, namely for inhibiting the expression of apolipoprotein B mRNA.

Therefore, the invention as a whole would have been prima facie obvious over Tang et al. in view of Branch, Monia et al. and Agrawal.

Conclusion

10. Claims 24-26 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Janet L. Epps-Ford, Ph.D. whose telephone number is 703-308-8883. The examiner can normally be reached on Monday-Thursday, 8:30 AM - 6:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader can be reached on 703-308-0447. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Janet L. Epps-Ford, Ph.D.
Examiner
Art Unit 1635

JLE